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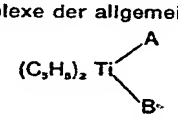
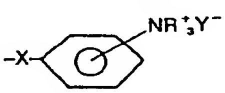
(54) **Cytostatisch wirksame Titanocen-Komplexe.**

(57) Titanocen-Komplexe der allgemeinen Formel I



(I)

in der A die Gruppe



bedeutet, wobei
X ein Sauerstoff- oder Schwefelatom ist,
R Wasserstoff oder eine C_{1-4}-Alkylgruppe ist und
Y ein Halogenid ist, oder die Gruppe –O–CO–R' bedeutet, wobei R' die Gruppe $-CF_3$, $-CCl_3$, $-CBr_3$, $-CHCl_2$, $-CH_2Cl$, –CH=CH–COOH oder $-(CH_2)_nCOOH$ ist und n den Wert 0, 1, 2, 3 oder 4 hat, und B ein Halogenid ist oder wie der Rest A definiert ist;
sind cystostatisch wirksam und eignen sich daher zur Krebsbekämpfung, insbesondere zur Behandlung von soliden Tumoren.

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Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.4)
D,Y	DE-A-2 923 334 (H. KÖPF et al.) * Ansprüche *	1,4-9	C 07 F 17/00 A 61 K 31/28
Y	EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, CHIMIE THERAPEUTIQUE, Band 19, Nr. 4, 1984, Seiten 347-352; P. KÖPF-MAIER et al.: "Tumorhemmung durch Metallocene: Titan-Komplexe des Typs [TiCp2XY] und [TiCpX2Y] * Insgesamt *	1,4-9	
P,X	INORGANICA CHIMICA ACTA, Band 108, 1985, Seiten 99-103; P. KÖPF-MAIER et al.: "New antitumor titanocene derivatives containing hydrophilic ligands" * Insgesamt *	1-10	
			RECHERCHIERTE SACHGEBIETE (Int. Cl.4)
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DEN HAAG	05-12-1986	BESLIER L.M.

KATEGORIE DER GENANNTEN DOKUMENTE

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(54) Title: NOVEL METALLOCENES AS ANTI-TUMOR DRUGS

(57) Abstract

The invention relates to novel titanocene derivatives possessing chemotherapeutic activity and method for their preparation. These compounds possess two cyclopentadiene rings linked to titanium as a central atom and bound covalently to two phenoxy groups which possess a substituent R selected from the group consisting of: $COOCH_3$, $COOC_2H_5$, H, $COOCH_2CH_2OCH_2CH_2OCH_3$ and are free from amino groups, nitro, chloride and fluoride. The novel compounds represent a compromise between the main properties for an antitumor agent, i.e. electrophilicity and stability, being water soluble. Cytotoxicity measurements of these compounds showed significant growth inhibition properties, expressed in terms of $IC_{50}[M]$ values.

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NOVEL METALLOCENES AS ANTI-TUMOR DRUGS

The present invention relates to new titanocene compounds. More particularly the invention relates to new titanocene complexes and methods for their preparation, which possess chemotherapeutic activity being useful for the treatment of human tumors.

BACKGROUND OF THE INVENTION

There are known metallocene complexes containing titanium, vanadium, niobium and molibdenum as a metal ion, which are active against a variety of tumor cell lines such as B16 melanoma, colon 38 carcinoma, Lewis lung carcinoma, etc. It has been shown that the activity of vanadium complexes related to the formula Cp_2VCl_2 where C_p is cyclopentadiene, against human epidermoid (HEP-2) tumor cells in vitro and against mouse tumor cells, is similar to that of cis-platin (Murthy M.S. et al. Proc. Am. Assoc. Cancer Res. 1986, 27, 279). A study which was carried out with a corresponding molibdenum compound, supports the possibility that these complexes are binding 5'-phosphate terminated polynucleotides, thus inhibiting DNA replication, by a mechanism which is different from that of cis-platinum complexes (Kon,L.Y. et al. J.Am. Chem.Soc. 1991, 113, 9027).

Titanocene dichloride, one of the first metallocene compounds which was tested, was found to be indeed a very reactive anti-tumor reagent. Due to its rapid hydrolysis

to the corresponding dihydroxy derivative, it is quite reasonable to assume that this dihydroxy titanocene is the actual drug. Accordingly, many references can be found describing titanocene compounds which were tested in an attempt to possess an improved cytotoxity. Examples of such compounds include halides, pseudohalides, carboxylates, and phenolates. However, no significant improvement over titanocene dichloride in the antitumor activity has been achieved.

The metallocene diacido complexes, having the general formula $(C_5H_5)_2MX_2$ are characterized by the following structural features:

- The geometry of the complexes is that of a distorted tetrahedron.
- The complexes contain two uninegative acido ligands X coordinated to the central metal atom and arranged in adjacent "cis-like" position.
- The sites of the other two ligands are occupied by two anionic cyclopentadienyl rings.

Attempts to modify the cyclopentadienide rings lead to a decreased biological activity.

In a very recent U.S. Patent No. 5,002,969 there are described cytostatic pharmaceutical compositions based on titanocene complexes. A group which is present in all these complexes is an amino or substituted amino bound to

the titancceno moiety. These compounds are obtained by a reaction between a titanocene dihalogenide and an amino phenol, lithium aminophenolate, or lithium amino thiophenolate. There is mentioned that the compcunds have a better solubility in water than titanocene dichloride, fact which improves their application and dosing.

Other titanocene complexes which were described, differ by their ionic character from the neutral titanocene compounds. Most of them correspond to the general formula $[(C_5H_5)_2TiXL]^+Y^-$ where X and Y are anions and L is a neutral donor molecule. These ionic titanocene complexes are characterized by their improved water solubility compared with the neutral titanocene compounds.

It is an object of the present invention to provide novel titanocene derivatives. It is another object of the present invention to provide novel titanocene derivatives which possess a superior cytotoxic activity than the cis-platinum complexes.

BRIEF DESCRIPTION OF THE INVENTION.

The invention relates tc novel titanocene derivatives which comprise two cyclopentadiene rings linked tc titanium as a central atom, which are bound covalently to two phenoxy groups which possess a substituent R which is selected from the group consisting of: $COOCH_3$, $COOC_2H_5$, H, $COOCH_2CH_2OCH_2CH_2OCH_3$ being free from amino groups,

nitro group, chloride and fluoride. The above novel titanocene derivatives represent a compromise between the two main properties required for an antitumor agent: electrophilicity and stability.

DETAILED DESCRIPTION OF THE INVENTION.

It is a generally accepted assumption that titanocenes, as well as other antitumor agents, do react with DNA in a similar manner. Therefore, the two main properties required for the drugs, in addition to the water solubility, are electrophilicity and stability in order to survive the aqueous biological medium during the time required to reach the target. The inventor's approach was to synthesize the new compounds which should possess these two main properties. Accordingly, the titanocene compounds envisaged should contain groups such as phenolates, having the role of moderate leaving groups, and appropriate substituents on the phenyl rings which impart stability to these compounds. Thus, considering the electrophilic role played by the metallocene drug in binding to the nucleophilic sites of polynucleotides, it may be concluded that an optimal biological activity would be achieved when the titanocene compounds, according to the present invention, will contain leaving groups of moderate reactivity, such as phenols substituted at their 4-position with $COOCH_3$, $CO_2CH_2CH_2CH_2OCH_2CH_2OCH_3$, CH_2-CH_3,

$COCH_3$, H and of course possessing a satisfactory hydrolytic stability.

Typical examples of the novel titanocene derivatives are as follows:

1. Bis(4-cyanophenolato)bis(n^5-cyclopentadienyl)titanium (IV), hereinafter referred to as TCN.
2. Bis(4-methoxycarbonylphenolato)bis(n^5-cyclopentadienyl)titanium(IV), hereinafter referred to as TPE
3. Bis(4-ethoxycarbonylphenolato)bis(n^5-cyclopentadienyl) hereinafter referred to as TEE1.
4. Bis[4-(2-methoxyethoxy)ethoxy]carbonylphenolato]bis-(n^5-cyclopentadienyl)titanium(IV),hereinafter referred to as TEG.
5. Bis[4-(methoxy)ethoxycarbonylphenolato]bis(n^5cyclopentadienyl)titanium(IV), hereinafter referred to as TMEM.
6. Bis[4-(2-dimethylamino)ethoxycarbonylphenolato]bis-(n^5-cyclopentadienyl)titanium(IV), hereinafter referred to as TCA.
7. Bis[4-(2-trimethylammono)ethoxycarbonylphenolato]bis-(n^5cyclopentadienyl)titanium(IV), hereinafter referred to as TCE.

Cytotoxicity measurements carried out with the above compounds show significant growth inhibition properties of these compounds expressed in terms of IC_{50}[M] values.

In the following Table 1 are presented the results which show that these compounds are much superior than the known titanocene dichloride (TDC) under the same conditions. The value of the ratio Ti/Pt represents the relative activity of TPE as compared with that of cis-platinum. The first four entries represent data of normal cell lines and the other ten entries represent the experiments with tumor cell lines.

TABLE 1. Cytotoxic data of titanocene derivatives.

Cell line	Cell type	TPE	TDC	cisPt	Ti / Pt
CHO	Chinese Hamstead Ovary	1.3×10^{-5}	10^{-3}	3.1×10^{-5}	2
HMEC	Normal Human Mammary	3.1×10^{-6}	1.3×10^{-4}	6.3×10^{-5}	20
NHDF	Normal Human Skin	1.6×10^{-6}	10^{-3}	3.1×10^{-5}	20
NHEK	Normal Keratino Epithelial	3.1×10^{-6}	10^{-3}	6.3×10^{4}	200
Capan 1	Pancreas Carcinoma	3.9×10^{-7}	5.0×10^{-4}	3.9×10^{-6}	10
HT-29	Colon Carcinoma	3.9×10^{-4}	5.0×10^{-4}	1.3×10^{-4}	200
SK-Mel-28	Melanoma	1.6×10^{-6}	10^{-3}	1.6×10^{-5}	10
H-322	Lung Carcinoma	6.3×10^{-7}	10^{-3}	6.3×10^{-5}	100
UCLA-P3	Lung Carcinoma	3.1×10^{-6}	10^{-3}	6.3×10^{-5}	20
MCF-7	Breast Cancer	2.0×10^{-6}	10^{-3}	1.3×10^{-4}	100
HL-60	B-cell Leukemia	3.1×10^{-6}	10^{-3}	7.8×10^{-6}	2
Molt-4	T-cell Leukemia	-10^{-6}	10^{-3}	-10^{-5}	10
Ovcar-3	Ovarian Carcinoma	6.3×10^{-6}	10^{-3}	6.3×10^{-5}	10
P-388	Mouse Leukemia	3.9×10^{-6}	5.0×10^{-4}	9.8×10^{-7}	025

The cytotoxicity results with a number of titanocene derivatives, expressed in concentrations (M) are presented in the attached Table 2 for a number of solid tumors. For combating solid tumors, the titanocene derivatives according to the present invention may be employed as such or as pharmaceutical compositions containing at least one titanocene complex as described above in addition to pharmaceutically acceptable excipients, diluents and/or auxiliary agents. The excipient can serve as an agent for promoting absorption of the medicament by the body or as formulation auxiliary, sweetener, flavouring agent, colourant or preservative. The pharmaceutical formulations of the active compounds are preferably in the form of unit doses matched to the particular mode of administration. The amount of the active compound is chosen so that one or more units are usually sufficient for an individual therapeutic administration. In addition to that, the medicaments with the active compound, may contain also one or more other pharmacologically active constituents, such as: alkylating agents, antimetabolites antibiotics, vitamins, enzymes and heavy metal compounds. The novel titanocene derivatives, according to the present invention, can be prepared from common chemical reagents using standard equipment. It should be realized, that the Examples for their preparations presented

hereinafter are only for illustration and many other routes may be conceived for their syntheses.

EXAMPLE 1. Preparation of Bis(4-cyanophenolato)bis (η^5-cyclopentadienyl)titanium(IV) TCN.

An amount of 238 mg(2mmol) of 4-cyanophenol was dissolved in 10 ml of benzene and 200 mg of sodium hydride 80% in mineral oil (6.67mmol) was added and stirred at room temperature for about 10 minutes. To this mixture an amount of 249 mg (1mmol) of titanocene dichloride was added and the mixture refluxed for 8 hours, cooled to room temperature and placed on a short column containing silica gel (pre-washed with acetone). The elution with methylene chloride followed by removal of the solvent under reduced pressure, yielded crude TCN. By purifying the crude TCN on a chromatographic column (silica gel, ethyl acetate-hexane), an amount of 290 mg of pure TCN (70% yield) was obtained in the form of a yellow solid. The analysis of the product on ^1H NMR ($CDCl_3$) was as follows:

7.52 (d,J=8.6Hz,4H), 6.64(d,J=8.6Hz, 4Hz), 6.31(s, 10H).

EXAMPLE 2. Preparation of Bis(methoxycarbonylphenolato) bis(η^5-cyclopentadienyl)titanium(IV) TPE.

In the same manner as in Example 1, an amount of 273mg (2 mmol) of methyl 4-hydroxybenzoate was reacted with 249 mg

(1mmol) of titanocene dichloride. An amount of 364 mg of TPE (81% yield) in the form of a yellow solid was obtained.

The analysis of the product on ^1H NMR ($CDCl_3$) was as follows:

7.91 (d, J=8.7 Hz, 4H), 6.64 (d, J=8.7Hz, 4H), 6.33 (s, 10H), 2.56 (s, 6H).

EXAMPLE 3. Preparation of Bis(4-ethoxycarbonylphenolato)-bis(n^5-cyclopentadienyl)titanium(IV) TEE1.

In the same manner as in Example 1, an amount of 332mg (2mmol) of ethyl 4-hydroxybenzoate was reacted with 249mg (1 mmol) of titanocene dichloride. An amount of 417 mg of TEE1 (81% yield) was obtained.

The analysis of the product on ^1H NMR ($CDCl_3$) was as follows:

7.90 (d, J=8.6 Hz, 4H), 6.61 (d, J=8.6Hz, 4H), 6.31 (s, 10H), 2.94 (q, J=7.3Hz, 4H), 1.21 (t, J=7.3 Hz, 6H).

EXAMPLE 4. Preparation of Bis[4-(2-(2-methoxyethoxy) ethoxy]carbonylphenolato]bis(n^5-cyclopentadienyl)titanium(IV) TEG

(a) In a first step, an amount of 1g (43 mmol) of sodium was dissolved in 25 ml of 2-(2-methoxyethoxy)ethanol. To the resulted solution an amount of 3 g (22mmol) of methyl 4-hydroxybenzoate was added and the mixture was heated tc

130^{o}C for 24 hours; after cooling to room temperature, it was acidified with a hydrochloric acid solution (3N) and extracted with ethyl acetate. The removal of the sclvent under reduced pressure and column chromatography of the residue (silica gel, hexane:ethyl acetate 3:1) afforded 2-(2-methoxyethoxy)ethyl 4-hydroxybenzoate, in the fcrm of a colourless oil in essentially quantitative yield.

(b) In the second step, an amount of 480 mg (2mmol) of the product obtained in step (a), was reacted with 249 mg (1mmol) of titanocene dichloride, as describted in Example 1. An amount of 355 mg of TEG (54% yield) was obtained. The analysis of the product on ^{1}H NMR ($CDCl_3$) was as follows:

7.95 (d, J=8.6 Hz, 4H), 6.60 (d, J=8.6 Hz, 4H)
6.31 (s, 10H), 4.45 (t, J=5.0Hz, 4H),
3.83 (t,J=5.0Hz, 4H), 3,70 (t, J=4.6 Hz, 4H),
3.57 (t, J=4.6 Hz, 4H), 3.38(s, 6H).

EXAMPLE 5:Preparation of Bis[4-(2-methoxy)ethoxycarbonyl-phenolato]bis(η^5-cyclopentadienyl)titanium(IV) TMEM.

(a) In the first step (as in the Example 4) 1 g (43 mmol) of sodium was dissolved in 25 ml of 2-methoxyethanol. An amount of 3.0 g (22 mmol) of methyl 4-hydroxy-benzoate was added, producing 2-methoxyethyl 4-hydroxybenzoate, as a colourless oil, in essentially quantitative yield.

(b) In the second step, an amount of 392 mg (2mmol) of the product obtained in step (a) was reacted with 249 mg (1.1 mmol) of titanocene dichloride as described above in Example 1, affording 330 mg of TMEM (58% yield). The analysis of the product on ^1H NMR ($CDCl_3$) was as follows:

7.96 (d, J=8.6 Hz, 4H), 6.60 (d, J=8.6 Hz, 4H),
4H), 6.29 (s, 10H), 4.42 (t, J=4.8 Hz, 4H),
3.70 (t, J=4.8 Hz, 4H), 3.70 (t, J=4.8 Hz, 4H),
3.40 (s, 6H).

EXAMPLE 6: Preparation of Bis[4-(2-dimethylamino)ethoxycarbonylphenolato]bis(η^5-cyclopentadienyl) titanium(IV) TCA

(a) In a first step, 1 g (43mmol) of sodium was dissolved in 20 ml of 2-(dimethylamino)ethanol. An amount of 3.0 g (22 mmol) of methyl 4-hydroxybenzoate was added and heated to 110°C for 24 hours and then cooled to room temperature. The solvent was removed under reduced pressure and using a column chromatography (silica gel, chloroform - methanol), a white solid of 2-(dimethylamino)-ethyl 4-hydroxybenzoate was obtained.

(b) In the second step, an amount of 418 mg (2 mmol) of the product obtained in step (a) was reacted with 249 mg (1mmol) of titanocene dichloride, as described in Example 1, affording 330 mg of TCA (58% yield).

The analysis of the product on ^{1}H NMR ($CDCl_3$) was as follows:

7.94 (d, J=8.6 Hz, 4H), 6.59 (d, J=8.6Hz, 4H), 6.30 (s, 10H), 4.39 (t, J=7.2 Hz, 4H), 2.71 (t, J=7.2Hz, 4H), 2.34 (s, 12H).

EXAMPLE 7: Preparation of Bis[4-(2-trimethylamino)ethoxy-carbonylphenolato]bis(η^5-cyclopentadienyl) titanium(IV).

The TCA product as obtained in the previous Example 6, was treated with an excess of methyl iodide (10 equiv) in benzene for about 6 hours. A yellow solid of TCE is formed, collected by filtration, washed by benzene and ether and dried.

The analysis of the product on ^{1}H NMR (DMSO) was as follows:

7.87 (d, J=8.6 Hz, 4H), 6.66 (d, J=8.6 Hz, 4H), 6.44 (s, 10H), 4.64 (m, 4H), 3.77 (m, 4H), 3.18 (s, 18H).

TABLE 2: DATA ON CYTOTOXICITY (log).

	Column 1	Column 2	cis-platin	TEG	TMEM	TEE-1	TCE	TPE	TP
1	CHOChin. Harm.Ov.		-4.51		-4.30	-4.60		-4.80	-4.20
2	HMEC	Nor.Hum.	-4.20		-4.60	-6.11		-5.70	-3.89
3	NHDF	Nor.Humn Skin	-4.51		-4.30	-4.89		-5.41	-4.51
4	Capan-1	Pan (a)	-5.41		-4.89	-5.51	-4.00	-6.41	-4.20
5	HT-29	Colon car.	-3.89		-4.60	-5.20	-4.00	-5.41	-4.20
6	SK ML-28	Melanoam	-4.80		-4.60	-5.51		-5.41	-3.89
7	H-322	Lung Car.	-4.20		-4.89	-5.80	-4.00	-6.20	-4.20
8	UCLA-P3	Lung Car.	-4.20			-5.20		-5.51	-3.89
9	MCF-7	Mamary Car.	-3.89		-4.89	-5.80	-4.30	-5.70	-4.20
10	HL-60	Leukemia	-5.11		-4.60	-5.51		-5.70	-3.30
11	Molt-4	Leukemia	-5.00	-4.00	-7.00	-7.00	-4.00	-6.00	-4.00
12	P-388	Mouse	-6.01			-4.89		-5.41	-4.20
13	NHEK	Normal	-3.20			-5.80		-5.51	
14	Ovar-3	Ovarian car.	-4.20	-4.00	-4.60	-5.20	-4.00	-5.20	-3.89
15	SIHA	Cerv. Carc.			-4.60		-4.00		
16	MCF-7 (Adr)	Adri (b)			-5.51				
1	-3.00	-3.00	-3.00	-3.00		-4.00	-4.60	-3.00	-4.30
2	-3.30	-3.00	-3.00	-3.00		-4.60	-5.20	-3.89	-4.00
3	-3.30	-3.00	-3.00	-3.00		-4.00	-4.00	-3.00	-4.00
4	-3.60	-3.00	-3.00	-3.00		-4.30	-5.51	-3.30	-4.30
5	-3.60	-3.30	-3.30	-3.00		-4.00	-4.89	-3.30	-4.30
6	-3.30	-3.00	-3.00	-3.00		-4.60	-5.51	-3.00	-4.00
7	-3.30	-3.00	-3.00	-3.00	-4.00	-4.30	-4.30	-3.00	-4.30
8	-3.60	-3.00	-3.00	-3.00	-4.30			-3.00	
9	-3.30	-3.00	-3.00	-3.00	-4.30	-4.89	-4.89	-3.00	-4.30
10	-3.00	-3.60	-3.00	-3.00	-4.00	-4.00	-5.80	-3.00	-4.00
11	-2.00	-3.00	-3.00	-3.00		-4.00	-4.00	-3.00	-4.00
12	-3.60	-3.00	-3.00	-3.00	-5.00			-3.30	
13								-3.00	
14	-3.60	-3.00	-3.00	-3.00		-4.30	-5.51	-3.00	-4.00
15						-4.30	-4.30		-4.30
16									

(a) Pancrease Car.
(b) Adriyamicin.

C L A I M S :-

1. Novel titanocene derivatives which comprise two cyclopentadiene rings linked to titanium as a central atom, which are bound covalently to two phenoxy groups which possess a radical substituent R which is selected from the group consisting of:

H, $COOCH_3$, $COOC_2H_5$, $COOCH_2CH_2OCH_2CH_2OCH_3$,

being free from amino group, nitro group, chloride and fluoride.

2. The novel titanocene derivatives according to Claim 1, which possess chemotherapeutic activity being used for the treatment of tumors.

3. Bis(4-cyanophenolato)bis(n^5-cyclopentadienyl)titanium (IV).

4. Bis(4-methoxycarbonylphenolato)bis(n^5-cyclopentadienyl)titanium(IV).

5. Bis(4-ethoxycarbonylphenolato)bis(n^5-cyclopentadienyl)titanium(IV).

6. Bis(4-[2-(methoxyethoxy)ethoxy]carbonylphenolato)bis (n^5- cyclopentadienyl)titanium(IV).

7. Bis[4-(2-methoxy)ethoxycarbonylphenolato]bis(η^5-cyclopentadienyl)titanium(IV).

8. Bis[4-(2-dimethylamino)ethoxycarbonylphenolato]bis-(η^5-cyclopentadienyl)titanium(IV).

9. Bis[4-(2-trimethylamino)ethoxycarbonylphenolato]-bis(η^5-cyclopentadienyl)titanium(IV).

10. The novel titanocene derivatives according to Claim 1, to be applied as medicaments in combination with other pharmaceutically active constituents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/07875

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/28; C07F 17/00, 7/28
US CL :556/53, 55; 514/492
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 556/53, 55; 514/492

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

N/A

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY DATA BASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Organometallic Chemistry, Volume 11, No. 3, issued March 1968, K. Andra, "Dicyclopentadienyltitan-diphenoxide" pages 567-570. see page 567, especially table I, compound (II).	1
A	US, A, 5,002,969 (Kopf-Maier et al) 26 March 1991, see entire document.	1-10
Y	R. Feld et al., "The Organic Chemistry of Titantium" published 1965 by Butterworths Inc. (Washington, D.C.), see pages 3-15, especially page 5, reaction equation No. 1.13.	1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 18 NOVEMBER 1993	Date of mailing of the international search report 06 DEC 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer PORFIRIO NAZARIO-GONZALEZ Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/U[illegible]/07875

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	P.C. Wailes et al., "Organometallic Chemistry of Titanium, Zirconium, and Hafnium", published 1974 by Academic Press (N.Y.), see pages 62-73.	1-10